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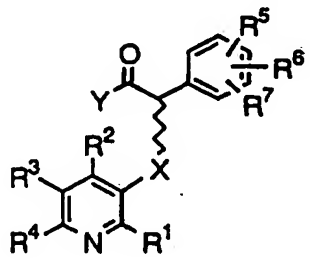
(54)Title: NOVEL PHENYLACETIC ACID DERIVATIVES AND MEDICINAL COMPOSITION CONTAINING THE SAME

(54)発明の名称 新規フェニル酢酸誘導体およびそれを含有する医薬組成物



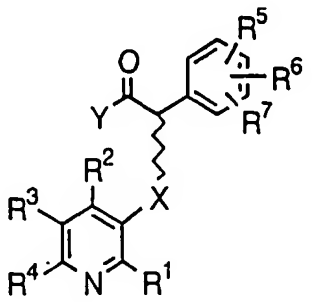
(I)

(57) Abstract

Compounds represented by general formula (I), amine oxides thereof, pharmaceutically acceptable salts thereof, or hydrates thereof, and medicinal compositions comprising the same, wherein R^1 to R^7 represent each hydrogen, halogeno, optionally substituted lower alkyl, etc; and X represents -O-, -S- or $-NR^{15}$ wherein R^{15} represents hydrogen or optionally substituted lower alkyl. The compounds are a potent endothelin receptor antagonist and thus highly useful in the treatment or prevention of diseases caused by endothelin.

（５７）要約

下記一般式（Ｉ）：



(I)

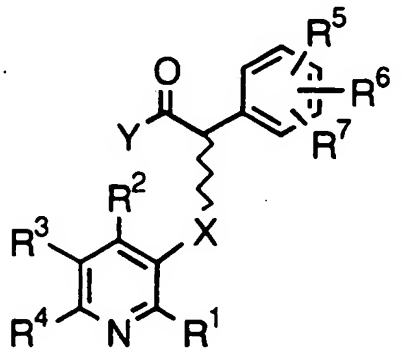
（ただし、Ｒ¹からＲ⁷は水素、ハロゲン、置換可低級アルキル等、Ｘは－Ｏ－、－Ｓ－または－ＮＲ¹³－（Ｒ¹³は水素または置換可低級アルキル））で示される化合物、そのアミンオキサイドもしくはそれらの製薬上許容される塩またはそれらの水和物およびそれを含有する医薬組成物に関する。本発明化合物は強力なエンドセリン受容体拮抗剤であり、エンドセリンに起因する疾患の治療または予防に非常に有用である。

[SPECIFICATION] New phenylacetic-acid derivative and pharmaceutical composition which contains it

[TECHNICAL FIELD] This invention relates to compound useful as a pharmaceutical, and its application.
In more detail, it is related with new phenylacetic-acid derivative useful for prevention and treatment of illness in which endothelin participates, and its intermediate.

[DESCRIPTION OF RELATED ART] Endothelin is vasoconstriction peptide derived from vascular endothelial cell which consists of 21 amino acids.
It participates in homeostasis of blood vessel.
For example, endothelin acts through endothelin receptor as an exacerbation factor of illness of circulating systems, such as hypertension, cerebrovascular contraction, acute renal failure, acute fecundity nephropathy, acute myocardial infarction, cerebral infarction, kidney ischemia, myocardial ischemia, cerebral ischemia, endothelial hypertrophy, and subarachnoid hemorrhage.
Moreover, exerting a certain effect on internal-secretions tissues in addition to circulating system, such as central nervous system and pituitary gland, and suprarenal body, is known.
Some compounds which have similar structure in compound which has endothelin receptor antagonism are known (Unexamined-Japanese Patent 6211810, WO94/21590, WO95/03295, WO95/26710, etc.).
However, development of endothelin receptor antagonist with higher activity and useful to clinical is desired.

[DISCLOSURE OF THE INVENTION] Present inventors did earnest examination that forceful endothelin receptor antagonist should be developed.
As a result, compound shown by the following formula(I) discovered attaining this objective, and perfected this invention.
That is, this invention is formula(I). :



(I)

(In the Formula, R1 is lower alkyl which may
have hydrogen, halogen, and substituent, lower alkenyl which may have substituent, cycloalkyl which may have substituent, aryl which may have substituent, heteroaryl which may have substituent, lower alkoxy which may have substituent, lower alkylthio which may have substituent, lower alkoxy carbonyl, carboxy which may have substituent, lower acyl which may have substituent, amino which may have substituent
Hydrazono lower alkyl, hydroximino lower alkyl, lower alkoxy imino lower alkyl, carbamyl which may have substituent, carbamyl lower alkyl which may have substituent, carbamyl oxy lower alkyl which may have substituent, - NHCOR8 or -NHSO2 R8 (aryl which may have lower alkyl in which R8 may have substituent here, or substituent).
R2 and R3 are aryls which may have lower alkyl which may have hydrogen, halogen, and substituent respectively independently, or substituent.
R4 is lower alkyl and -NHCOR8' (aryl which may have lower alkyl in which R8' may have substituent here, or substituent) which may have hydrogen, halogen, and substituent, lower alkoxy carbonyl which may have substituent, acyl which may have substituent, carboxy, nitrile, hydrazono lower alkyl, hydroximino lower alkyl, lower alkoxy imino lower alkyl, carbamyl which may have substituent, carbamyl lower alkyl which may have substituent, aryl which may have carbamyl oxy lower alkyl or substituent which may have substituent.

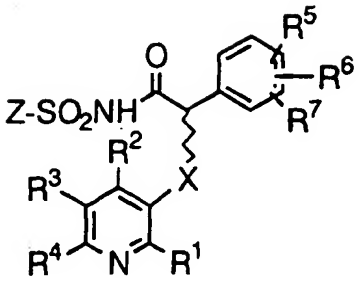
R5, R6 and R7 are lower alkyls which may have hydrogen, halogen, and substituent respectively independently, lower alkenyl which may have substituent, lower alkoxy which may have substituent, aryl which may have substituent, carboxy, lower alkoxy carbonyl which may have substituent, amino which may have hydroxy, nitro, and substituent
Carbamyl which may have substituent, and -NHCOR8 ", -NHS02 R8" (aryl which may have lower alkyl in which R8" may have substituent here, or substituent), or -SOnR9 (R9 whose n is integer of O-2 here is lower alkyl)
Or R5 and R6 adjoin mutually, it becomes together and they are -W-CR10=CR11- and -W-CR10=N-, - W-N=CR10-, -W-(CR12 R12) m-W'-, -W-CR12 R12-CR12 R12-, -CR10=CR11-W-, -N=CR10-W-, -CR12RI2-CR12 R12-W-, -CR10=CR11CR10=CR11 -
(W and W' is -O-, -SOp-, or -NR13- respectively independently here.
R10 and R11 are lower alkyls which may have hydrogen and substituent respectively independently, lower alkenyl which may have substituent, cycloalkyl which may have substituent, halogen, carboxy, lower alkoxy carbonyl that may have substituent, carbamyl which may have substituent, amino which may have substituent
-NHCOR8" or -NHS02 R8" (R8" is same meaning as the above mentioned here), lower alkoxy which may have substituent, -SOnR9 (n and R9 are same meaning as the above mentioned here), or -SO2NR13 R14.
R12 is lower alkyl which may have hydrogen and substituent, lower alkenyl which may have substituent and hydroxy, amino, carboxy which may have substituent, lower alkoxy carbonyl which may have substituent, or -NHCOR8" (R8" is same meaning as the above mentioned here).

R13s are lower alkyl which may have hydrogen
and substituent, and cycloalkyl which may have aryl which may have substituent, or substituent.
R14 is lower alkyl which may have substituent, aryl which may have substituent, cycloalkyl which may have substituent, or tetrazolyl which may have substituent.
M is 1 or 2.
P is integer of O-2.)
It may form the above, x is -O-, -S-, or -NR15- (lower alkyl in which R15 may have hydrogen or substituent here).
Y is hydroxy or -NHSO2-Z (Z is aryl which may have substituent, or heteroaryl which may have substituent here).
Wavy line shows that X replaced at least by benzyl is R arrangement, S arrangements, or those mixed arrangements.)
Compound shown by these, its amine oxide, those pharmaceutically acceptable salts, or those hydrates are provided.
Moreover, this invention provides pharmaceutical composition and endothelin receptor antagonist which contain compound (I), particularly.
This invention administers compound (I) as another aspect.
It is related with prevention of illness in which endothelin participates and/or the method of treatment which are characterized by the above-mentioned.
Furthermore, it is related with use of compound for medicinal manufacture for prevention and/or treatment of illness in which endothelin participates (I).

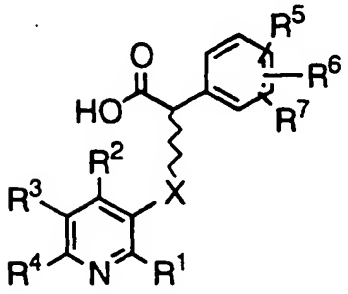
[PREFERRED EMBODIMENT OF THE INVENTION] "Halogen" means fluorine, chlorine, bromine, and iodine in this specification.
"Lower alkyl" in lower-alkyl j which may have "substituent means linear or branched C1-6 alkyl group, methyl, ethyl, n- propyl, isopropyl, n- butyl, iso butyl, sec-butyl, tert- butyl, n- pentyl, isopentyl, neopentyl, hexyl, etc. are included specifically.
Particularly C1-4 alkyl is desirable and in particular methyl, ethyl, and propyl are desirable.
These groups may have 1 or more substituents, such as halogen, hydroxy, carboxy, lower alkoxy carbonyl, lower alkoxy, lower acyl, lower acyloxy, and amino, trialkylsilyl oxy, in desired positions.
"Lower alkenyl" in "lower alkenyl which may have substituent" means linear or branched C2-7 alkenyl, for example, vinyl, allyl, propenyl, isopropenyl, butenyl, butadienyl, pentenyl, pentadienyl, hexenyl, hexa dienyl, heptanyl, hepta dienyl, etc. are mentioned.
These may have 1 or more double bond in desired positions, and these may have 1 or more substituent in desired positions.
The substituent is the same as that of thing of the above-mentioned lower alkyl.
"Cycloalkyl" in "cycloalkyl which may have substituent" means C3-8 cyclic alkyl, cyclopropyl, cyclo butyl, cyclopentyl, cyclohexyl, cyclo heptyl, and cyclooctyl are included.
These may have 1 or more substituent of lower-alkyl, halogen, hydroxy, carboxy, lower alkoxy carbonyl, lower alkoxy, lower acyl, lower acyloxy, and amino etc. in desired positions.

In particular cyclopropyl, cyclo butyl, and cyclopentyl are desirable.
"Aryl" in "aryl which may have substituent" includes phenyl, naphthyl, 1,2,3,4-tetrahydro naphthyl, indanyl, etc. specifically.
These may have 1 or more substituents, such as lower-alkyl, halogen, hydroxy, carboxy, lower alkoxy carbonyl, lower alkoxy, lower acyl, lower acyloxy, and amino, lower-alkyl amino, lower alkoxy carbonyl, cycloalkyl, and phenyl, in desired positions.
It is phenyl which may preferably have substituent.
"Heteroaryl" in "heteroaryl which may have substituent" means heteroaryl which has hetero atom chosen from O, S, and N as desired one or more endocyclic.
It is heteroaryl of 5-6 members, such as pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, isoxazolyl, oxazolyl, oxadiazolyl, iso thiazolyl, thiazolyl, thiadiazolyl, furyl, and thienyl, specifically, condensation heteroaryls, such as indolyl, benz imidazolyl, indazolyl, indolizinyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, naphthyldinyl, quinoxalinyl, pterdinyl, benz isoxazolyl, benz oxazolyl, oxadiazolyl, benz iso thiazolyl, benz thiazolyl, benz thiadiazolyl, benzofuryl, and benzo thienyl, are mentioned.
In particular thienyl is desirable.
These may all have 1 or more substituent in desired positions, and the substituent is the same as that of thing of the above-mentioned aryl.
However, in particular lower alkoxy carbonyl is desirable.
"Lower acyl" in "lower acyl which may have substituent" includes acyl which may have double bond and/or substituent in positions linear C1-6 or branched, and desired.
Formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, iso valeryl, pivaloyl, acryloyl, methacryloyl, crotonoyl, etc. are mentioned specifically.
These may have 1 or more substituent in desired positions, and the substituent is the same as substituent of the above "lower alkyl which may have substituent."
Definition of "lower acyl" part in "lower acyloxy" is the same as that of "lower acyl" of the above "lower acyl which may have substituent."
"Amino which may have substituent" includes unsubstituted or substituted amino.
As the substituent, lower alkyl which may have substituent, aryl which may have substituent, heteroaryl which may have substituent are mentioned.
Substituent of "carbamyl which may have substituent", and "carbamyl oxy which may have substituent" is the same as substituent of the above "amino which may have substituent."
Each lower-alkyl part and substituent of "lower alkoxy which may have substituent", "lower alkylthio which may have substituent", "lower alkoxy carbonyl which may have substituent", "hydrazono lower alkyl", "hydroximino lower alkyl", and "lower alkoxy imino lower alkyl" are the same as that of definition in the above "lower alkyl which may have substituent."

All compounds shown by said Formula (I) have endothelin receptor antagonism. However, preferably they are formula(II) and formula (III) :



(II)



(III)

(In the Formula, R1-R7, X and Z, and wavy line are same meaning as the above mentioned)

They are compound shown by these, its amine oxide, those pharmaceutically acceptable salts, or those hydrates.

Furthermore, in said Formula (II) and formula (III),

(1) Compound whose R1 is carbamyl or -NHSO2 R8 which may have amino which may have lower acyl which may have lower alkylthio which may have lower alkyl which may have hydrogen and substituent, cycloalkyl which may have substituent, aryl which may have substituent, lower alkoxy which may have substituent, and substituent, and substituent, and substituent, and substituent, compound which is lower alkylthio which may have lower alkoxy which may have lower alkyl which may have hydrogen and substituent further preferably, cycloalkyl which may have substituent, aryl which may have substituent, and substituent, or substituent, compound which is lower alkylthio which may have lower alkyl which may have substituent further preferably, cycloalkyl which may have substituent, aryl which may have substituent, or substituent, compound which is lower alkyl which may have substituent most preferably,

(2) Compound whose R2 and R3 are lower alkyls which may have hydrogen or substituent respectively independently, compound whose each is hydrogen further preferably,

(3) Compound whose R4 is aryl which may have carbamyl oxy lower alkyl or substituent which may have lower alkyl which may have hydrogen and substituent, lower alkoxy carbonyl which may have substituent, acyl which may have substituent, nitrile, hydrazono lower alkyl, hydroximino lower alkyl, lower alkoxy imino lower alkyl, carbamyl that may have substituent, and substituent, compound which is aryl which may have lower alkyl which may have hydrogen and substituent further preferably, or substituent, compound which is lower alkyl which may have hydrogen or substituent most preferably,

(4) Lower alkyl in which R5, R6 and R7 may have hydrogen, halogen, and substituent respectively independently, lower alkenyl which may have substituent, lower alkoxy which may have substituent, compound with which R5 and R6 which are amino A which may have lower alkoxy carbonyl and hydroxy which may have carboxy and substituent, nitro, or substituent, or adjoin become together, and form -W-(CR12 R12) m-W'-, further preferably, compound which R5 and R6 which are lower alkoxy or nitro with which R5, R6 and R7 may have

lower alkyl which may have hydrogen, halogen,
and substituent respectively independently, and substituent, or adjoin become together, and forms -W-(CR12 R12) m-W'-,
(5) Compound whose X is -O-,
(6) Compound which is thienyl which may have indanyl which may have phenyl in which Z may have substituent, naphthyl which may have substituent, 1,2,3,4-tetrahydro naphthyl which may have substituent, and substituent, or substituent, compound which is aryl which may be replaced further preferably by lower-alkyl, halogen, lower alkoxy, and lower-alkyl amino, lower alkoxy carbonyl or cycloalkyl, compound which is phenyl which may be replaced by lower alkyl most preferably.

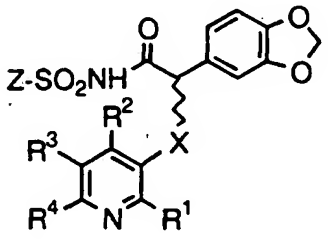
(7) R2 and R3 are lower alkyls which may have hydrogen or substituent respectively independently.
Compound whose R4 is aryl which may have carbamyl oxy lower alkyl or substituent which may have lower alkyl which may have hydrogen and substituent, lower alkoxy carbonyl which may have substituent, acyl which may have substituent, nitrile, hydrazono lower alkyl, hydroximino lower alkyl, lower alkoxy imino lower alkyl, carbamyl that may have substituent, and substituent,

(8) R1 is carbamyl or -NHSO2 R8 which may have amino which may have lower acyl which may have lower alkylthio which may have lower alkyl which may have hydrogen and substituent, cycloalkyl which may have substituent, aryl which may have substituent, lower alkoxy which may have substituent, and substituent, and substituent, and substituent, and substituent.
R2 and R3 are lower alkyls which may have hydrogen or substituent respectively independently.
Compound whose R4 is aryl which may have carbamyl oxy lower alkyl or substituent which may have lower alkyl which may have hydrogen and substituent, lower alkoxy carbonyl which may have substituent, acyl which may have substituent, nitrile, hydrazono lower alkyl, hydroximino lower alkyl, lower alkoxy imino lower alkyl, carbamyl that may have substituent, and substituent,
(9) R1 is lower alkylthio which may have lower alkoxy which may have lower alkyl which may have hydrogen and substituent, cycloalkyl which may have substituent, aryl which may have substituent, and substituent, or substituent.
R2 and R3 are hydrogen respectively.
R4 is aryl which may have lower alkyl which may have hydrogen and substituent, or substituent.
Compound whose X is -O-, further preferably, R1 is lower alkylthio which may have lower alkyl which may have substituent, cycloalkyl which may have substituent, aryl which may have substituent, or substituent.
R2 and R3 are hydrogen respectively.
R4 is lower alkyl which may have hydrogen or substituent.
Compound whose X is -O-,
(10) R1 is carbamyl or -NHSO2 R8 which may have amino, substituent which may have lower acyl which may have lower alkylthio which may have lower alkyl which may have hydrogen and substituent, cycloalkyl which may have

substituent, aryl which may have substituent,
lower alkoxy which may have substituent, and substituent, and substituent, and substituent.
R2 and R3 are lower alkyls which may have hydrogen or substituent respectively independently.
R4 is aryl which may have carbamyl oxy lower alkyl or substituent which may have lower alkyl which may have hydrogen and substituent, lower alkoxy carbonyl which may have substituent, acyl which may have substituent, nitrile, hydrazono lower alkyl, hydroximino lower alkyl, lower alkoxy imino lower alkyl, carbamyl that may have substituent, and substituent.
X is O.
Compound whose Z is thienyl which may have indanyl which may have phenyl which may have substituent, naphthyl which may have substituent, 1,2,3,4-tetra pi mud naphthyl which may have substituent, and substituent, or substituent, lower alkylthio which may, further preferably, have lower alkyl in which R1 may have substituent, cycloalkyl which may have substituent, aryl which may have substituent, or substituent.
R2 and R3 are lower alkyls which may have hydrogen or substituent respectively independently.
R4 is aryl which may have lower alkyl which may have hydrogen and substituent, or substituent.
X is -O-.
Compound whose Z is aryl which may be replaced by lower-alkyl, halogen, lower alkoxy, and lower-alkyl amino, lower alkoxy carbonyl, or cycloalkyl, most preferably, R1 is lower alkyl which may have substituent.
R2 and R3 are hydrogen respectively.
R4 is lower alkyl which may have hydrogen or substituent.
X is -O-.
Compound whose Z is aryl which may be replaced by lower-alkyl, halogen, lower alkoxy, and lower-alkyl amino, lower alkoxy carbonyl or cycloalkyl,

(11) R1 is carbamyl or -NHSO2 R8 which may have vulgarity which may have lower alkylthio which may have lower alkyl which may have hydrogen and substituent, cycloalkyl which may have substituent, aryl which may have substituent, lower alkoxy which may have substituent, and substituent, and substituent, amino which may have substituent, and substituent.
R2 and R3 are lower alkyls which may have hydrogen or substituent respectively independently.
R4 is aryl which may have carbamyl oxy lower alkyl or substituent which may have lower alkyl which may have hydrogen and substituent, lower alkoxy carbonyl which may have substituent, acyl which may have substituent, nitrile, hydrazono lower alkyl, hydroximino lower alkyl, lower alkoxy imino lower alkyl, carbamyl that may have substituent, and substituent.
Lower alkyl in which R5, R6 and R7 may have hydrogen, halogen, and substituent respectively independently, lower alkenyl in which it may have substituent, lower alkoxy which may have substituent, carboxy, lower alkoxy carbonyl and hydroxy which may have substituent, nitro, or amino which may

have substituent
Or adjoining R5 and adjoining R6 become together, and form -W-(CR12 R12) m-W'-, x is O.
Compound which is thienyl which may have indanyl in which Z may have phenyl which may have substituent, naphthyl in which it may have substituent, 1,2,3,4-tetrahydro naphthyl which may have substituent, and substituent, or substituent, further preferably, lower alkylthio which may have lower alkyl in which R1 may have substituent, cycloalkyl which may have substituent, aryl which may have substituent, or substituent.
R2 and R3 are lower alkyls which may have hydrogen or substituent respectively independently.
R4 is aryl which may have lower alkyl which may have hydrogen and substituent, or substituent.
R5, R6 and R7 are lower alkyl which may have hydrogen, halogen, and substituent respectively independently, lower alkoxy which may have substituent, or nitro, or adjoining R5 and adjoining R6 become together, and form -W-(CR12 R12) m-W'-, x is -O-.
Compound whose Z is aryl which may be replaced by lower-alkyl, halogen, lower alkoxy, and lower-alkyl amino, lower alkoxy carbonyl or cycloalkyl, most preferably, R1 is lower alkyl which may have substituent.
R2 and R3 are hydrogen respectively.
R4 is lower alkyl which may have hydrogen or substituent.
R5, R6 and R7 are lower alkyl which may have hydrogen, halogen, and substituent respectively independently, lower alkoxy which may have substituent, or nitro, or adjoining R5 and adjoining R6 form -W-(CR12 R12) m-W'- together, x is -O-.
Compound which is aryl by which Z may be replaced by lower-alkyl, halogen, lower alkoxy, and lower-alkyl amino, lower alkoxy carbonyl, or cycloalkyl is desirable.
More preferably, they are formula (II') and formula (III'). :



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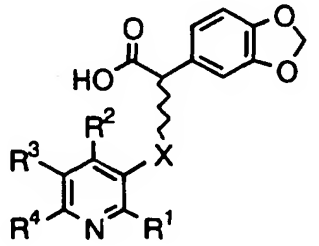


(III')

(In the Formula, R1-R4, X and Z, and wavy line are same meaning as the above mentioned)
They are compound shown by these, its amine oxide, those pharmaceutically acceptable salts, or those hydrates.
Most preferably, it is following.

In said Formula (II'),

(1) Compound whose R1 is carbamyl or -NHSO2
R8 which may have amino A which may have lower acyl which may have lower alkylthio which may have lower alkyl which may have hydrogen and substituent, cycloalkyl which may have substituent, aryl which may have substituent, lower alkoxy which may have substituent, and substituent, and substituent, and substituent, and substituent, compound which is lower alkylthio which may have lower alkoxy which may have lower alkyl which may have hydrogen and substituent further preferably, cycloalkyl which may have substituent, aryl which may have substituent, and substituent, or substituent, compound which is lower alkylthio which may have lower alkyl which may have substituent further preferably, cycloalkyl which may have substituent, aryl which may have substituent, or substituent, compound which is lower alkyl which may have substituent most preferably,
(2) R2 and R3 are compounds which are lower alkyl which may have hydrogen or substituent respectively independently, compound whose each is hydrogen further preferably,
(3) Compound whose R4 is aryl which may have carbamyl oxy lower alkyl or substituent which may have lower alkyl which may have hydrogen and substituent, lower alkoxy carbonyl which may have substituent, acyl which may have substituent, nitrile, hydrazono lower alkyl, hydroximino lower alkyl, lower alkoxy imino lower alkyl, carbamyl that may have substituent, and substituent, compound which is aryl which may have lower alkyl which may have hydrogen and substituent further preferably, or substituent, compound which is lower alkyl which may have hydrogen or substituent most preferably,
(4) Compound whose X is -O-,
(5) Compound which is thienyl which may have indanyl in which Z may have phenyl which may have substituent, naphthyl in which it may have substituent, 1,2,3,4-tetrahydro naphthyl which may have substituent, and substituent, or substituent, compound which is aryl which may be replaced further preferably by lower-alkyl, halogen, lower alkoxy, and lower-alkyl amino, lower alkoxy carbonyl or cycloalkyl, compound which is phenyl which may be replaced by lower alkyl most preferably,
(6) R2 and R3 are lower alkyls which may have hydrogen or substituent respectively independently.
Compound whose R4 is aryl which may have carbamyl oxy lower alkyl or substituent which may have lower alkyl which may have hydrogen and substituent, lower alkoxy carbonyl which may have substituent, acyl which may have substituent, nitrile, hydrazono lower alkyl, hydroximino lower alkyl, lower alkoxy imino lower alkyl, carbamyl that may have substituent, and substituent,
(7) R1 is carbamyl or -NHSO2 R8 which may have amino, substituent which may have lower acyl which may have lower alkylthio which may have lower alkyl which may have hydrogen and substituent, cycloalkyl which may have substituent, aryl which may have substituent, lower alkoxy which may have substituent, and substituent, and substituent, and substituent.
R2 and R3 are lower alkyls which may have hydrogen or substituent respectively independently.
Compound whose R4 is aryl which may have carbamyl oxy lower alkyl or

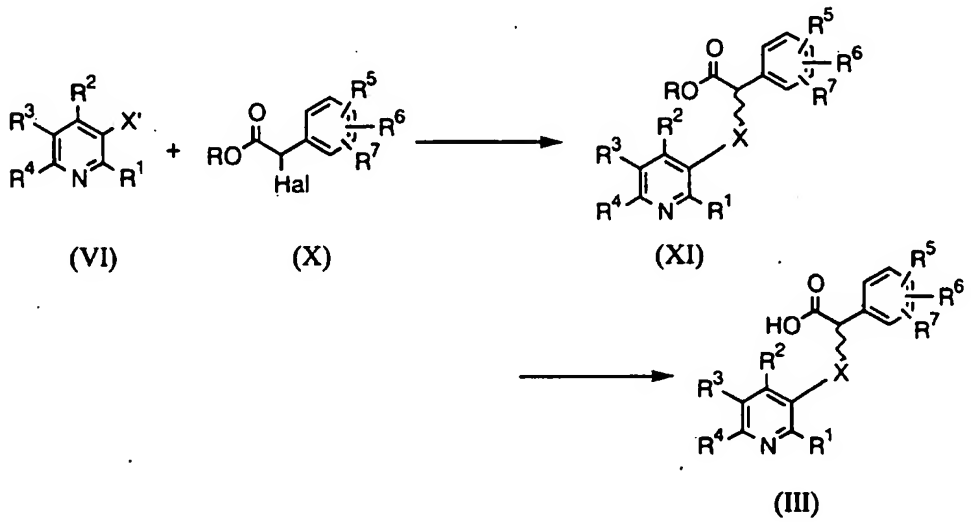
substituent which may have lower alkyl which
may have hydrogen and substituent, lower alkoxy carbonyl which may have substituent, acyl which may have substituent, nitrile, hydrazono lower alkyl, hydroximino lower alkyl, lower alkoxy imino lower alkyl, carbamyl that may have substituent, and substituent, further preferably R1 is lower alkylthio which may have lower alkoxy which may have lower alkyl which may have hydrogen and substituent, cycloalkyl which may have substituent, aryl which may have substituent, and substituent, or substituent.
R2 and R3 are hydrogen respectively.
Compound whose R4 is aryl which may have lower alkyl which may have hydrogen and substituent, or substituent,
(8) R1 is lower alkylthio which may have lower alkoxy which may have lower alkyl which may have hydrogen and substituent, cycloalkyl which may have substituent, aryl which may have substituent, and substituent, or substituent.
R2 and R3 are hydrogen respectively.
R4 is aryl which may have carbamyl oxy lower alkyl or substituent which may have lower alkyl which may have hydrogen and substituent, lower alkoxy carbonyl which may have substituent, acyl which may have substituent, nitrile, hydrazono lower alkyl, hydroximino lower alkyl, lower alkoxy imino lower alkyl, carbamyl that may have substituent, and substituent.
Compound whose X is -O-, further preferably R1 is lower alkylthio which may have lower alkyl which may have substituent, cycloalkyl which may have substituent, aryl which may have substituent, or substituent.
R2 and R3 are hydrogen respectively.
R4 is aryl which may have lower alkyl which may have hydrogen and substituent, or substituent.
Compound whose X is -O-,
(9) R1 is lower alkylthio which may have lower alkoxy which may have lower alkyl which may have substituent, cycloalkyl which may have substituent, aryl which may have substituent, and substituent, or substituent.
R2 and R3 are lower alkyls which may have hydrogen or substituent respectively independently.
R4 is aryl which may have carbamyl oxy lower alkyl or substituent which may have lower alkyl which may have hydrogen and substituent, lower alkoxy carbonyl which may have substituent, acyl which may have substituent, nitrile, hydrazono lower alkyl, hydroximino lower alkyl, lower alkoxy imino lower alkyl, carbamyl that may have substituent, and substituent.
X is -O-.
Compound whose Z is thienyl which may have indanyl which may have phenyl which may have substituent, naphthyl which may have substituent, 1,2,3,4-tetrahydro naphthyl which may have substituent, and substituent, or substituent, further preferably R1 is lower alkylthio which may have lower alkoxy which may have lower alkyl which may have substituent, cycloalkyl which may have substituent, aryl which may have substituent, and substituent, or substituent.
R2 and R3 are lower alkyls which may have hydrogen or substituent respectively independently.
R4 is aryl which may have lower alkyl which may have hydrogen and

substituent, or substituent.
X is -O-.
Compound whose Z is aryl which may be replaced by lower-alkyl, halogen, lower alkoxy, and lower-alkyl amino, lower alkoxy carbonyl or cycloalkyl, further preferably R1 is lower alkylthio which may have lower alkyl which may have substituent, cycloalkyl which may have substituent, aryl which may have substituent, or substituent.
R2 and R3 are hydrogen respectively.
R4 is aryl which may have lower alkyl which may have hydrogen and substituent, or substituent.
X is -O-.
Compound whose Z is aryl which may be replaced by lower-alkyl, halogen, lower alkoxy, and lower-alkyl amino, lower alkoxy carbonyl or cycloalkyl, most preferably, R1 is lower alkyl which may have substituent.
R2 and R3 are hydrogen.
R4 is lower alkyl which may have hydrogen or substituent.
X is -O-.
Compound which is aryl by which Z may be replaced by lower alkyl,

(10) N- (4-isopropyl phenyl sulfonyl>-(alpha)-(diethyl -3- pyridyloxy) -1,3-benzene di oxole -5- acetamide, N-(4-isopropyl phenyl sulfonyl)-(alpha)-(2-n-propyl- 3-pyridyloxy) -1,3- benzene di oxole -5- acetamide)
N-(4-isopropyl phenyl sulfonyl)-(alpha)-(6-methyl-2-n- propyl- 3-pyridyloxy) -1,3-benzene oxole -5- acetamide.
Compound chosen from group which consists of the above, in said Formula (III'), (1) Compound whose R1 is carbamyl or -NHS02 R8 which may have amino which may have lower acyl which may have lower alkylthio which may have lower alkyl which may have hydrogen and substituent, cycloalkyl which may have substituent, aryl which may have substituent, lower alkoxy which may have substituent, and substituent, and substituent, and substituent, and substituent, compound which is lower alkyl which may have substituent further preferably,
(2) Compound which is lower alkyl in which R2 and R3 may have hydrogen or substituent respectively independently, compound whose each is hydrogen further preferably,
(3) Compound which is aryl in which R4 may have lower alkyl which may have hydrogen and substituent, or substituent, compound which is lower alkyl which may have hydrogen or substituent further preferably,
(4) Compound whose X is -O-,
(5) R1 is carbamyl or -NHSO2 R8 which may have amino, substituent which may have lower acyl which may have lower alkylthio which may have lower alkyl which may have hydrogen and substituent, cycloalkyl which may have substituent, aryl which may have substituent, lower alkoxy which may have substituent, and substituent, and substituent, and substituent.
R2 and R3 are lower alkyls which may have hydrogen or substituent respectively independently.
R4 is aryl which may have lower alkyl which may have hydrogen and

substituent, or substituent.
Compound whose X is -O-, further preferably R1 is lower alkyl which may have substituent.
R2 and R3 are hydrogen respectively.
R4 is lower alkyl which may have hydrogen or substituent.
Compound whose X is -O-
These are desirable.

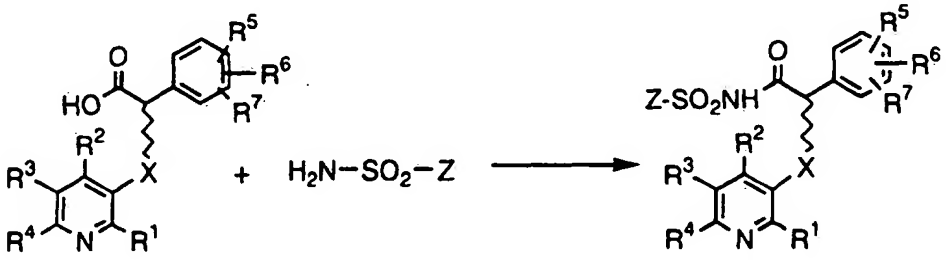
When calling it "this invention compound" and it is made, the pharmaceutically acceptable salt is also included.
For example, salt with alkali metals (sodium, potassium, lithium, etc.), alkaline-earth metal (calcium, magnesium, etc.), ammonium or organic base, amino acid, etc., and salt with inorganic acid (hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, etc.) or organic acids (acetic acid, citric acid, maleic acid, fumaric acid, benzenesulfonic acid, p toluenesulfonic acid, etc.) are mentioned.
These salts can be formed by method usually performed.
Moreover, the amine oxide is also included to this invention compound.
Furthermore, this invention compound also includes the hydrate, it may form water and hydrate more than 1 molecule to this invention compound 1 molecule.
Optical isomer exists in this invention compound.
However, both R arrangement S arrangements and those mixed arrangements exist within the range of this invention.
In particular R arrangement is desirable.
This invention compound (I), i.e., compound (II) and (III), can be manufactured, for example by the following method.



(In the Formula, R1-R7 is same meaning as the above mentioned.
X' is -OH, -SH, or -NHR16.
Ha1 is halogen.

R is lower alkyl.)
In this manufacturing method, compound (VI) and (X) are condensed on suitable conditions, and compound (XI) is obtained, it is hydrolyzed by usual method and compound (III) is obtained.
What is sufficient is just to make condensing reaction react under room-temperature-heating, preferably near room temperature in solvent, such as dimethylformamide, acetonitrile, and acetone, in the presence of bases, such as potassium carbonate, sodium carbonate, potassium hydroxide, and sodium hydroxide
For several-hours-24 hours, preferably about 2 to 5 hours.

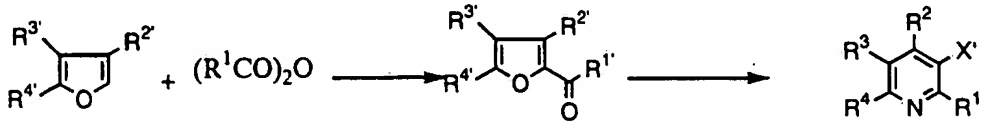
Hydrolysis dissolves compound (XI) in lower alcohols, such as methanol and ethanol, bases, such as suitable concentration, for example, 1-N sodium hydroxide, or potassium hydroxide aqueous solution, are added, and while cooling - heating, if it is preferably made to react 1 hour to 24 about hour near room temperature, compound (HI) will be obtained.



(III) (XII) (II)

Next, carboxyl group of compound (111) melted into solvent is activated, while cooling - heating, preferably, it is sulfonamides compound (it is made to condense with XID and compound (II) is obtained.) near room temperature by base presence.
What is sufficient is just to use tetrahydrofuran, diethyl ether, dimethoxyethane, methylene chloride, 1,2- dichloroethane, etc. as solvent.
For example, 1,1'- carbonyl-di imidazole is used for activation of carboxyl group.
As a base, for example, 1,8- diazabicyclo [5.4.0] undec -7- en can be used conveniently.
After using this invention compound (III) obtained by the above-mentioned method as quaternary salt with chiral amine if it is required since it is racemic body, it can obtain optically active substance by dissociating from acid.
For example, this invention compound (III) of racemic body and chiral amines, such as (R)-(+)-(alpha)- methyl benzylamine, (1S, 2R)-(+)-norephedrine, (1S, 2S)-(+) -2- amino- 1-phenyl- I, 3-propanediol, and D-threo- (-)-2-amino- 1-(4-nitrophenyl) -1,3- propanediol, after dissolving to organic solvents, such as ethyl acetate, acetonitrile, methanol, ethanol, and isopropanol, solvent is distiled and quaternary salt of R arrangement of this invention compound (III) is obtained by repeating recrystallization with the above-mentioned solvent.

Furthermore, compound of R arrangement of this
invention compound (III) is obtained by dissociating this quaternary salt with organic acids, such as inorganic acid, such as hydrochloric acid and sulfuric acid, or acetic acid, and oxalic acid.
Moreover, if optical resolution is performed by similar method using chiral amines, such as (S)-(-)-(alpha)- methyl benzylamine and (1R, 2S)-(-)-norephedrine, compound of S arrangement of this invention compound (III) will be obtained.
Thus, if obtained optically active this invention compound (III) is used, optically active substance of this invention compound (II) can also be obtained suitably.
Well-known compound, or compound which may be derived by usual method from public knowledge thing may be used for compound (VI) and (X) used for the above-mentioned synthesis method, compound compounded by the still more nearly following method can also be used.



(IV) (V) (VI)

(R1'-R4' is group which can be respectively converted into R1-R4 by usual method here)
Compound (VI) is obtained, for example by the following method.
First, public knowledge compound, or compound obtained by well-known method (IV)
Is reacted at 0 degree C-100 degree C, preferably 40 degree C-60 degree C for several-hours-several days, preferably 1 hour - about 24 hours,
It acylates and compound (V) is obtained.
Next, let compound (V) react by suitable alcohol or suitable ammonium hydroxide of ammonia containing, etc. under room-temperature-heating
Preferably 150 degrees C or more, several-hours-several days, preferably 10 hour - about 48 hours.

Compound (VI) which is X'=OH is obtained.
Specifically, compound (IV) is made to react by acylating agents, such as acid anhydride (for example, n- butyric-acid anhydride, propionic anhydride) corresponding to target compound, or acid chloride (for example, 4-tert- butyl benzenesulfonyl chloride, acetyl chloride, propionyl chloride), under 0 degree C-heating, preferably 40 degree C-60 degree C, it acylates, and compound (V) is obtained.
As long as it is required here, it may use buffers, such as phosphoric acid.
Next, compound (VI) which is X'=OH can be obtained by mixing and heating with ammonia containing ethanol or ammonium-hydroxide solution.
Commercial item may be used for compound (VI) which is X'=NHR16, it can also obtain as a by-product of the above-mentioned method of manufacturing

compound (VI) which is X'=OH.
In obtaining compound (VI) which is X'=SH, it carries out thio carbamoylation of the compound (VI) which is X'=OH by method generally used, it attaches to rearrangement reaction, what is necessary is to form carbamyl thio and just to convert into X'=SH finally.

Specifically, thio carbamoylation agents, such as assisting agents, such as dimethylamino pyridine, and dimethyl thio carbamyl chloride, by base presences, such as inside of solvent, such as acetone, methyl ethyl ketone, and acetonitrile, triethylamine, and N- methyl morpholine, it is made to react several-hours several -days, near room temperature preferably at 0 degree C- heating, and thio carbamyl is obtained.
Next, rearrangement reaction is performed at high temperature 200 degrees C or more with high-boiling-point solvent, such as diphenylether and dough sum, and it is considered as carbamyl thio, after making alkali-metal-ized agents, such as sodium hydride and potassium hydride, and saponifiers, such as 1-propane thiol, react several minutes at ice-cooling-room temperature during solvent, such as tetrahydrofuran, diethyl ether, and dimethoxyethane, furthermore, pyridine compound according to objectives, such as 3-dimethyl carbamyl thio- 2-n- propyl pyridine, is added, and target compound will be obtained if it is made to react several several-hours-days at ice-cooling-room temperature.
If substituent R1'-R4' of compound (IV) and compound (V) is group which can be converted into substituent R1-R4 of compound (VI) eventually made into objective by method usually performed, either is possible for it.
Substituent R1'-R4' is convertible for substituent R1-R4 in suitable phase using chemical reaction usually used, for example, the following reaction.
When obtaining compound (VI) whose X' is OH and whose substituents in any one of R1-R4 are sulfonamides, X' is OH first.
Preferably several minute-several-hours reaction of compound (VI) whose any of substituent is Amino A, and the sulfonylation agents, such as 4-tert-butylbenzene sulfonyl chloride and methane sulfonyl chloride, is carried out near room temperature under ice-cooling-heating in solvent of pyridine and DMF etc., and compound which sulfonylated X' is obtained, in solvent, such as tetrahydrofuran, diethyl ether, and dimethoxyethane, if several minute-several-hours reaction is carried out anion-ized agents, such as n- butyl-lithium hexane, at -80 degree C-0 degree C preferably near -70 degree C, target compound is obtained.
When any of substituent obtains compound (VI) which is alkoxy, any of substituent should just make compound (VI) which is halogen react several several-hours-days in base presences, such as sodium hydride and potassium hydride, during solvent, such as DMF and tetrahydrofuran, by alcohol, such as methanol and ethanol, at 0 degree C- heating, preferably near 110 degree C.
Compound (VI) whose any of substituent is -SH when obtaining compound (VI) whose any of substituent is lower alkylthio, what is sufficient is just to carry out several minute-several-hours reaction under alkylating agents, such as ethyl iodide and bromo-ized propyl, and room-temperature-heating, preferably near

80 degree C in solvent, such as acetonitrile and tetrahydrofuran

When any of group obtains compound (VI) which is acyloxy lower alkyl, any of group makes oxidizing agents, such as meta-chloro perbenzoic acid, hydrogen peroxide/acetic acid, peracetic acid, trifluoro peracetic acid, perbenzoic acid, and dimethyl dioxirane, react to compound (VI) which is lower alkyl, and obtains amine oxide compound, it may make it react under room-temperature-heating with usual acylating agents, such as several dozen minutes-several hours, acetic anhydride, and anhydrous trifluoroacetic acid.

Moreover, compound (VI) whose any of group is hydroxy lower alkyl and acylating agent similar to the above, as long as it is required, it may make it react at ice-cooling-room temperature, several-hours-several dozens of hours, with solvent, such as methylene chloride and dichloromethane.

When any of group obtains compound (VI) which is hydroxy lower alkyl, any of group should just make bases, such as sodium hydride and potassium hydride, react to compound which is acyloxy lower alkyl during solvent, such as methanol and ethanol.

When any of substituent obtains compound (VI) which is lower alkoxy lower alkyl, any of substituent carries out several-hours reaction of the halogenating agents, such as compound (VI) which is hydroxy lower alkyl, thionyl chloride, phosphoryl chloride, and chlorinated oxalyl, at ice-cooling-0 degree C, preferably ice cooling.

What is sufficient is just to make it react with alcohol according to objectives, such as methanol and ethanol, in base presences, such as metallic sodium, in solvent, such as toluene, benzene, chloroform, and methylene chloride.

When compound whose any of group is carbamyl oxy lower alkyl (VI) is obtained, what is sufficient is just to carbamolylate compound whose any of group is hydroxy lower alkyl (VI) by usual method in solvent, such as acetonitrile and tetrahydrofuran, using carbamoylation agents, such as several hours, chloro sulfonyl isocyanate, and trichloro acetyl isocyanate, at -50 degree C-room temperature.

When any of group obtains compound (VI) which is aldehyde, any of group should just perform DMS0 oxidation for compound (VI) which is hydroxy lower alkyl at -80 degree C- room temperature during solvent, such as dichloromethane and tetrahydrofuran, using acetic anhydride, anhydrous trifluoroacetic-acid, and SO3-pyridine, 2(COC1)-triethylamine, DCC-trifluoroacetic acid, and P2O5 grade as activator.

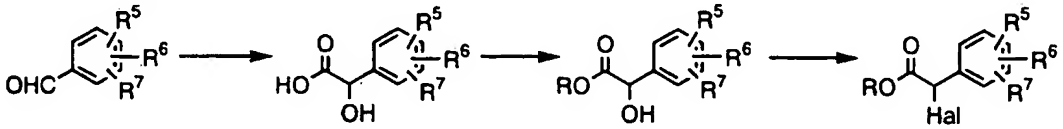
Moreover, it may oxidize using oxidizing agents, such as PCC, PDC, MnO2, and KMnO4.

When obtaining compound (VI) which is lower alkyl by which any of group was replaced by imino or hydrazone, any of group is mixed with several dozen minutes-several hours, and amino compounds, such as hydroxylamine, O-methyl hydroxylamine, and hydrazine, and should just make compound (VI) which has aldehyde react at ice-cooling-room temperature in alcohol, such as methanol and ethanol.

When any of group obtains compound (VI) which is carboxy, what is sufficient is

just to oxidize compound with which any of group
has aldehyde in solvent, such as acetonitrile and tetrahydrofuran, and under ice-cooling-heating for several hours using sodium chlorite in the presence of hydrogen peroxide, sulfamic acid, and 2-methyl-2-butene.
In obtaining compound (VI) whose any of group is cyano, let first compound whose any of substituent is hydrogen (VI) be amine oxide compound by method similar to the above.
Methylation agents, such as dimethyl sulfuric acid and methyl iodide, are made to react to the compound, and it is considered as methoxide pyridinium compound, what is necessary is to make it react with cyanation agents, such as several-hours-several dozens of hours, sodium cyanide, and potassium cyanide, and just to cyanate under room-temperature-heating.
In this reaction, solvent amount can also be used for dimethyl sulfuric acid of methylation agent.
In obtaining compound whose any of group is lower-alkyl oxycarbonyl (VI), in solvent, such as methylene chloride and dichloromethane, any of group makes compound (VI) which is carboxy react with several dozen minutes-several hours, and halogenating agents, such as thionyl chloride and chlorinated oxalyl, at ice-cooling-room temperature, and makes it acyl chloride, then, what is sufficient is just to make it react with corresponding alcohol.

When compound whose any of group is carbamyl which may have substituent (VI) is obtained, in solvent, such as methylene chloride and dichloromethane, any of group makes compound which is carboxy react with halogenating agents, such as several dozen minutes-several hours, thionyl chloride, and chlorinated oxalyl, at ice-cooling-room temperature, and makes it acyl chloride, then, what is sufficient is just to make it react with amine compounds, such as ammonia and dimethylamine.
Compound (X) is compoundable by the following method, for example.



(VII) (VIII) (IX) (X)

First, public knowledge compound, or compound obtained by well-known method (VII), for example, piperonal and chloroform, are dissolved to suitable solvent, while heating in the presence of phase-transition agents, such as benzyl chloride triethyl ammonium and benzyl-bromide triethyl ammonium, preferably bases, such as sodium hydroxide and potassium hydroxide, are added dropwise near 50 degree C-70 degree C.
What is necessary is for amount of reaction compound just to perform dropwise addition over several several-hours-days.
As solvent, liquid mixture of organic solvents, such as ether and chloroform, and water is used.

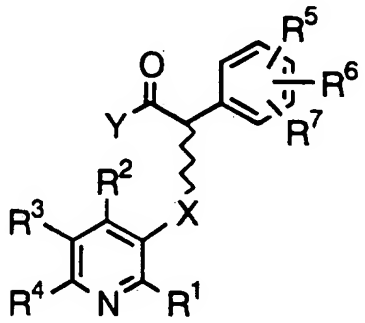
However, desirable organic solvent is chloroform
previously about reagent and solvent.
After that, acids, such as sulfuric acid and hydrochloric acid, neutralize this, and compound (VIII) is obtained.
Next, by heat-refluxing alcohol solutions, such as the methanol, ethanol, and propanol, in acid presences, such as sulfuric acid and hydrochloric acid, according to usual method, compound (VIII) is esterified and compound (IX) is obtained.
If reaction is performed under heating, preferably near 70 degree C-90 degree C, target compound will be obtained suitably.
Then, substitution reaction of hydroxy and halogen (Hal: for example, bromine, chlorine, iodine, etc.) is performed.
Substitution reaction of halogen adds dropwise solution of halogenating agents, such as thionyl chloride which dissolved in similar solvent, phosphorus trichloride, phosphorus oxychloride, phosphorus pentachloride, and phosphorus tribromide, into compound (IX) which dissolved in suitable solvent, such as methylene chloride, 1,2- dichloroethane, chloroform, and ethyl acetate, under cooling - room temperature,
What is sufficient is just to make it react for 10 to 20 hours preferably.
Compound (X) will be obtained if reaction product acquired here is extracted.
This invention compound (I), especially compound (II), has strong endothelin receptor antagonism, since it furthermore excels also in blood translatability, bioavailability is high and can constitute pharmaceutical which was very excellent.
Compound (III) is still more useful also as an intermediate of compound (II).
Therefore, each of these compounds are compounds useful as an endothelin receptor antagonist.
Since it is thought that endothelin receptor participates in expression of various illness including circulating system, this invention compound (I), its amine oxide, those pharmaceutically acceptable salts, or those hydrates are illness resulting from endothelin, for example, hypertension, coronary-artery illness, cardiac failure, kidney ischemia, myocardial ischemia, renal insufficiency, dialysis, cerebral ischemia, cerebral infarction, cerebral edema, migraine, subarachnoid hemorrhage, Raynaud syndrome, pulmonary hypertension, atherosclerosis, restenosis after balloon inducing blood-vessel enlargement, inflammation, gastric ulcer, duodenal ulcer, ulcuscruris ulcer (ulcuscruris), gram-negative sepsis, shock glomerulonephritis, renal colic, glaucoma, asthma, diabetic nephropathy, diabetes complication, complication in cyclosporin administration, etc.
It can be used for above-mentioned treatment and/or prevention.
This invention compound (1) and its salt, or hydrate can administer either oral or parenteral safely.
What is sufficient is just to administer oral administration by formulation usually used, such as powder, granule, tablet, pill, capsule, liquid agent, buccals, or sublingual drug.
Parenteral administration can administer suitably any formulation usually used, such as suppository, percutaneously absorbing agent, injectable solutions

(intramuscular injection, intravenous injection, etc.), and inhalant.
In particular as an administration route, oral administration is desirable.
Additive agents for pharmaceuticals, such as excipient appropriate to the formulation, binding agent, moistening agent, disintegrator, and lubricant agent, can be mixed as required to effective dose of this compound, and it can be considered as pharmaceutical formulation.
With carrier suitable in the case of injectable solution, sterilization is performed and it is considered as formulation.
Specifically, as excipient, they are lactose, saccharose, glucose, starch, calcium carbonate, or crystalline cellulose, as a binding agent, they are methylcellulose, carboxymethylcellulose, hydroxy-propyl cellulose, gelatin, or polyvinyl pyrrolidone, as a disintegrator, talc, magnesium stearate, or macrogol is mentioned as lubricant agents, such as carboxymethylcellulose, sodium carboxymethylcellulose, starch, sodium alginate, agar powder, or sodium lauryl sulfate.
Cocoa butter, macrogol, or methylcellulose can be used as a base of suppository.
Moreover, when preparing as liquid agent or milkiness, and a suspensible injectable solution, it may add suitably solubilizing agent usually used, suspending agent, emulsifier, stabilizer, preservative, isotonicity agent, etc., in oral administration, it may add corrigent, aromatic agent, etc.
As for dosage as a pharmaceutical of this invention compound, it is desirable to set up, after considering patient's age, body weight, administration route, kind, grade of illness, etc.
However, when orally administering to adult, it is usually 0.001 to 1000-mg/kg /day.
Preferably it is within the range of 0.01 to 10-mg/kg /day.
In the case of parenteral administration, it changes greatly with administration routes.
However, it is usually 0.001 to 100-mg/kg /day.
Preferably it is within the range of 0.01 to 10-mg/kg /day.
What is necessary is to divide this into 1 time-several times per day, and just to administer it.
Example and EXPERIMENT are given to below and this invention is demonstrated to it in detail.
However, this invention is not limited by these.

[EXAMPLES] Symbol used in this Example is as follows.
AcOEt
Bu
C-Bu
C-Pent
C-Pr
Et
Hept
Me

Ethyl acetate
Butyl
Cyclo butyl
Cyclopentyl
Cyclopropyl
Ethyl
Heptyl
Methyl

[CLAIMS] 1. Formula (1).



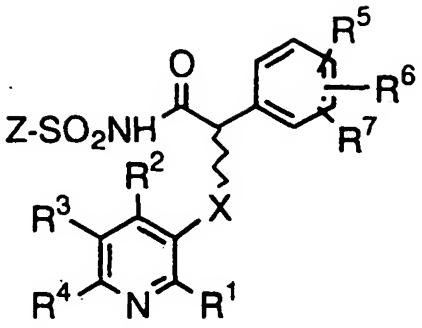
(I)

(In the Formula, R1 is lower alkyl which may have hydrogen, halogen, and substituent, lower alkenyl which may have substituent, cycloalkyl which may have substituent, aryl which may have substituent, heteroaryl which may have substituent, lower alkoxy which may have substituent, lower alkylthio which may have substituent, lower alkoxy carbonyl, carboxy which may have substituent, lower acyl which may have substituent, amino which may have substituent
Hydrazono lower alkyl, hydroximino lower alkyl, lower alkoxy imino lower alkyl, carbamyl which may have substituent, carbamyl lower alkyl which may have substituent, carbamyl oxy lower alkyl which may have substituent, - NHCOR8 or -NHSO2 R8 (aryl which may have lower alkyl in which R8 may have substituent here, or substituent).

R2 and R3 are aryls which may have lower alkyl which may have hydrogen, halogen, and substituent respectively independently, or substituent.
R4 is lower alkyl which may have hydrogen, halogen, and substituent, - NHCOR8' (aryl which may have lower alkyl in which R8' may have substituent here, or substituent), lower alkoxy carbonyl which may have substituent, acyl which may have substituent, carboxy, nitrile, hydrazono lower alkyl, hydroximino lower alkyl, lower alkoxy imino lower alkyl, carbamyl which may have substituent, carbamyl lower alkyl which may have substituent, carbamyl oxy lower alkyl which may have substituent, and these are aryls which may have substituent.
R5, R6 and R7 are lower alkyls which may have hydrogen, halogen, and

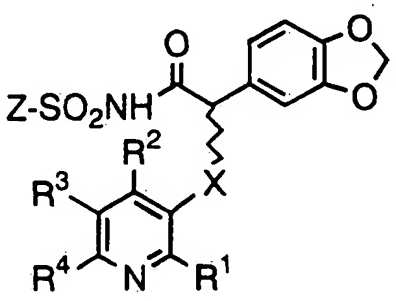
substituent respectively independently, lower alkenyl which may have substituent, lower alkoxy which may have substituent, aryl which may have substituent, carboxy, lower alkoxy carbonyl which may have substituent, carbamyl which may have amino which may have hydroxy, nitro, and substituent, and substituent, - NHCOR8 ", -NHSO2 R8"
(R8" is lower alkyl which may have substituent, or aryl which may have substituent here) Or it is -SOnR9 (R9 whose n is integer of 0-2 here is lower alkyl), or R5 and R6 adjoin mutually, it becomes together -W-CR10=CR11-, -W-CR10=N-, - W-N=CR10-, -W-(CR12 R12) m-W'-, -W-CR12 R12-CR12 R12 -, -CR10=CR11-W-, -N=CR10-W-, -CR12 R12-CR12 R12-W-, -CR10=CRl1CR10=CR11 - (W and W' is -O-, -SOp-, or -NR13- respectively independently here.
R10 and R11 are lower alkyls which may have hydrogen and substituent respectively independently, lower alkenyl which may have substituent, cycloalkyl which may have substituent, halogen, carboxy, lower alkoxy carbonyl that may have substituent, carbamyl which may have substituent, amino which may have substituent
- NHCOR8 "or -NHSO2 R8" (R8" is same meaning as the above mentioned here), lower alkoxy and -SOnR9 (n and R9 are same meaning as the above mentioned here) or -SO2NR13 R14 which may have substituent.
R12 is amino which may have lower alkyl which may have hydrogen and substituent, lower alkenyl which may have substituent, hydroxy, and substituent, carboxy, lower alkoxy carbonyl which may have substituent, or -NHCOR8" (R8" is same meaning as the above mentioned here).
R13 are lower alkyl which may have hydrogen and substituent, and cycloalkyl which may have aryl which may have substituent, or substituent.
R14 is lower alkyl which may have substituent, aryl which may have substituent, cycloalkyl which may have substituent, or tetrazolyl which may have substituent.
M is 1 or 2. P is integer of 0-2.)
It may form the above, x is -O-, -S-, or -NR15- (lower alkyl in which R15 may have hydrogen or substituent here).
Y is hydroxy or -NHSO2-Z (heteroaryl which may have aryl in which Z may have substituent here, or substituent).
Wavy line shows that X replaced at least by benzyl is R arrangement, S arrangements, or those mixed arrangements.)
Compound shown by these, its amine oxide, those pharmaceutically acceptable salts, or those hydrates.

2. Formula(II) :



(II)

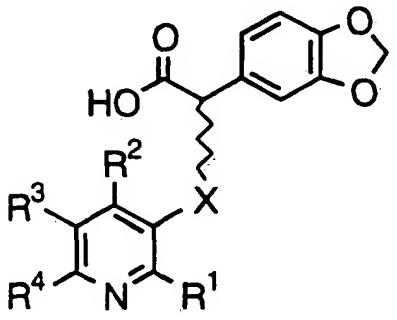
(In the Formula, R1-R7, X and Z, and wavy line are synonymous with Claim 1)
Compound shown by these, its amine oxide, those pharmaceutically acceptable salts, or those hydrates.
3. Formula (II') :



(II')

(In the Formula, R1-R4, X and Z, and wavy line are same meaning as the above mentioned)
Compound shown by these, its amine oxide, those pharmaceutically acceptable salts, or those hydrates.
4. R1 is lower alkyl which may have hydrogen and substituent, and cycloalkyl which may have substituent, aryl which may have substituent, lower alkoxy which may have substituent, lower acyl which may have lower alkylthio which may have substituent, and substituent, it is carbamyl or -NHSO2 R8 which may have amino which may have substituent, and substituent.
Compound of Claim 1, 2 or 3, the amine oxide, those pharmaceutically acceptable salts, or those hydrates.
5. R2 and R3 are lower alkyls which may have hydrogen or substituent respectively independently.
R4 is lower alkyl which may have hydrogen and substituent, and lower alkoxy carbonyl which may have substituent, acyl which may have substituent, nitrile, hydrazono lower alkyl, hydroximino lower alkyl, lower alkoxy imino lower alkyl, aryl which may have carbamyl oxy lower alkyl or substituent which may have carbamyl which may have substituent, and substituent.
Compound of Claim 1, 2 or 3, the amine oxide, those pharmaceutically acceptable salts, or those hydrates.

6. R1 is lower alkyl which may have hydrogen
and substituent, cycloalkyl which may have substituent, aryl which may have substituent, lower alkoxy which may have substituent, or lower alkylthio which may have substituent.
R2 and R3 are hydrogen respectively.
R4 is aryl which may have lower alkyl which may have hydrogen and substituent, or substituent.
X is -O-, compound of Claim 1, 2 or 3, the amine oxide, those pharmaceutically acceptable salts, or those hydrates.
7. Z is thienyl which may have indanyl which may have phenyl which may have substituent, the naphthyl which may have substituent, 1,2,3,4-tetrahydro naphthyl which may have substituent, and substituent, or substituent.
Compound, its amine oxide, those pharmaceutically acceptable salts, or those hydrates of Claim 2 or 3.
8. N-(4-isopropyl phenyl sulfonyl)-(alpha)- (diethyl -3- pyridyloxy)-1.3- benzene di oxole -5- acetamide)
N-(4-isopropyl phenyl sulfonyl)-(alpha)-(2-n- propyl- 3-pyridyloxy) -1,3- benzene di oxole -5- acetamide, n-(4-isopropyl phenyl sulfonyl)-(alpha)-(6-methyl-2-n-propyl- 3-pyridyloxy) -1,3- benzene oxole -5- acetamide, compound of Claim 1 chosen from group which consists of the above.
9. Formula (III') :



(III')

(In the Formula, R1, R2, R3, R4, X, and wavy line are same meaning as the above mentioned)
Compound shown by these, its amine oxide, those pharmaceutically acceptable salts, or those hydrates.
10.Pharmaceutical composition which contains compound in any one of Claim 1-9, its amine oxide, those pharmaceutically acceptable salts, or those hydrates as an active ingredient.
11. Endothelin receptor antagonist which contains compound in any one of Claim 1-9, its amine oxide, those pharmaceutically acceptable salts, or those hydrates as an active ingredient.
12. Administer compound in any one of Claim 1-9, its amine oxide, those pharmaceutically acceptable salts, or those hydrates.
The method of prevention and/or treatment of illness characterized by the above-mentioned that endothelin involves.

13. Use of compound in any one of Claim 1-9 for medicinal manufacture for prevention and/or treatment of illness in which endothelin participates, its amine oxide, those pharmaceutically acceptable salts, or those hydrates.

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